REMARKS

Claims 1 and 3-4 are currently under examination in the Application. Reconsideration is respectfully requested in view of the following remarks.

Claim Rejections – 35 U.S.C. § 101 (Utility) and 35 U.S.C. § 112, first paragraph (enablement)

Claims 1, 3 and 4 stand rejected under 35 U.S.C. § 101 because the claimed invention allegedly lacks patentable utility due to its not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility. The claims are also rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement since one of skill in the art would not know how to make and use the claimed invention due to its alleged lack of utility. In particular, the Action contends that just because a polynucleotide is overexpressed in certain tissues is not an indication of the polynucleotide being of diagnostic value, if it had not been shown that a correlation between the overexpression and disease is statistically significant. The Action notes that since only 30% of the cancer tissues show overexpression of the claimed sequence, then the claimed polynucleotide is not diagnostic of breast cancer. The Action further alleges that because the claimed polynucleotide is expressed in normal breast tissue as well as breast tumor tissue, this contradicts the notion that the protein expressed from the claimed polynucleotide could be used for diagnostic purposes.

Applicants respectfully traverse this rejection on the following grounds. Applicants respectfully note that:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility..." *In re Langer*, 503 F.2d 1391, 183 USPQ 297 (CCPA 1974; emphasis in original).

Furthermore, Applicants submit that it is not required to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965; emphasis added); *See also* MPEP 2107.02.

Moreover, an applicant need not provide evidence that establishes an asserted utility "as a matter of statistical certainty." Rather, a rigorous correlation is not necessary when a test is reasonably predictive of a result. *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980; emphasis added). Further still, in order to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (*i.e.*, "question") the truth of the statement of utility." (*e.g.*, MPEP 2107.02 IIIA; emphasis added). Applicants respectfully submit that this burden has not been met as no reasoned basis has been offered by the Examiner to establish that the skilled artisan would more likely than not question the position set forth by the Applicants.

When viewed in this light, Applicants submit that the claimed invention is adequately supported by a patentable diagnostic utility, and would be recognized as such by a skilled artisan in view of the instant disclosure.

With regard to the breast-specific expression pattern of the claimed polynucleotide of SEQ ID NO:305, Applicants respectfully submit that although differential overexpression of a sequence in tumor tissue versus normal tissue of the same tissue type is certainly one basis upon which a sequence can have diagnostic utility, the skilled artisan would appreciate that this is by no means the only basis. For example, a breast-specific sequence can be used in the detection of metastatic breast cancer cells that have escaped the site of a primary breast tumor. In this diagnostic scenario, expression of the sequence in normal breast tissue is inconsequential. The effectiveness of tissue-specific, as opposed to tumor-specific, polypeptides in the diagnosis of cancer, is further evidenced by the present widespread use of Prostate Specific Antigen (PSA), a prostate tissue-specific protein, to diagnose the presence of prostate cancer.

With regard to the Action's assertion that the polynucleotide of SEQ ID NO:305 is not diagnostic of breast cancer since only 30% of the cancer tissues show overexpression of the polynucleotide, Applicants respectfully direct the Office to Question 6 on page 4 of the enclosed copy of the National Cancer Institute Cancer Facts 5.29, where it is noted:

> Most men with an elevated PSA test turn out not to have cancer; only 25% to 30% of men who have a biopsy due to elevated PSA levels actually have prostate cancer." (emphasis added)

Applicants respectfully submit that the present invention is no less useful for the diagnosis of breast cancer than PSA is for the diagnosis of prostate cancer. Techniques for employing the inventive polynucleotides in the detection of breast cancer using blood-based assays are well known in the art, and include immunoassays, PCR-based assays and hybridization assays. It is urged that it would be well within the abilities of one of skill in the art, on being provided with the instant specification, to use the claimed polynucleotides in the detection of breast cancer.

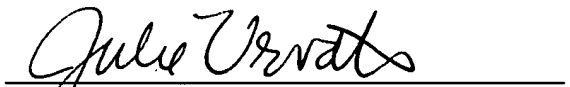
Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §§ 101 and 112.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all the claims remaining in the application are now believed allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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Enclosure:
Postcard
Copy of: National Cancer Institute Cancer Facts: The Prostate-Specific Antigen (PSA) Test: Questions and Answers

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NATIONAL CANCER INSTITUTE

Cancer Facts

Date reviewed: 08/17/2004

The Prostate-Specific Antigen (PSA) Test: Questions and Answers

Key Points

- Prostate-specific antigen (PSA) is a protein produced by the cells of the prostate gland. The PSA test measures the level of PSA in the blood (see Question 1).
- The U.S. Food and Drug Administration (FDA) has approved the use of the PSA test along with a digital rectal exam to help detect prostate cancer in men age 50 and older. The FDA has also approved the PSA test to monitor patients with a history of prostate cancer to see if the cancer has come back (recurred) (see Question 2).
- Doctors' recommendations for screening vary (see Question 3).
- The higher a man's PSA level, the more likely it is that cancer is present, but there are many other possible reasons for an elevated PSA level (see Questions 4 and 5).
- The PSA screening test has limitations and is still controversial (see Questions 6 and 7).

1. What is the prostate-specific antigen (PSA) test?

Prostate-specific antigen (PSA) is a protein produced by the cells of the prostate gland. The PSA test measures the level of PSA in the blood. The doctor takes a blood sample, and the amount of PSA is measured in a laboratory. Because PSA is produced by the body and can be used to detect disease, it is sometimes called a biological marker or tumor marker.

It is normal for men to have low levels of PSA in their blood; however, prostate cancer or benign (not cancerous) conditions can increase PSA levels. As men age, both benign prostate conditions and prostate cancer become more frequent. The most common benign prostate conditions are prostatitis (inflammation of the prostate) and benign prostatic hyperplasia (BPH) (enlargement of the prostate). There is no evidence that prostatitis or BPH cause cancer, but it is possible for a man to have one or both of these conditions and to develop prostate cancer as well.

PSA levels alone do not give doctors enough information to

distinguish between benign prostate conditions and cancer. However, the doctor will take the result of the PSA test into account when deciding whether to check further for signs of prostate cancer.

2. Why is the PSA test performed?

The U.S. Food and Drug Administration (FDA) has approved the PSA test along with a digital rectal exam (DRE) to help detect prostate cancer in men age 50 and older. During a DRE, a doctor inserts a gloved finger into the rectum and feels the prostate gland through the rectal wall to check for bumps or abnormal areas. Doctors often use the PSA test and DRE as prostate cancer screening tests; together, these tests can help doctors detect prostate cancer in men who have no symptoms of the disease.

The FDA has also approved the PSA test to monitor patients with a history of prostate cancer to see if the cancer has come back (recurred). An elevated PSA level in a patient with a history of prostate cancer does not always mean the cancer has come back. A man should discuss an elevated PSA level with his doctor. The doctor may recommend repeating the PSA test or performing other tests to check for evidence of recurrence.

It is important to note that a man who is receiving hormone therapy for prostate cancer may have a low PSA reading during, or immediately after, treatment. The low level may not be a true measure of PSA activity in the man's body. Men receiving hormone therapy should talk with their doctor, who may advise them to wait a few months after hormone treatment before having a PSA test.

3. For whom might a PSA screening test be recommended?

Doctors' recommendations for screening vary. Some encourage yearly screening for men over age 50, and some advise men who are at a higher risk for prostate cancer to begin screening at age 40 or 45. Others caution against routine screening, while still others counsel men about the risks and benefits on an individual basis and encourage men to make personal decisions about screening. Currently, Medicare provides coverage for an annual PSA test for all men age 50 and older.

Several risk factors increase a man's chances of developing prostate cancer. These factors may be taken into consideration when a doctor recommends screening. Age is the most common risk factor, with nearly 70 percent of prostate cancer cases occurring in men age 65 and older (1). Other risk factors for prostate cancer include family history, race, and possibly diet. Men who have a father or brother with prostate cancer have a greater chance of developing prostate cancer. African American men have the highest rate of prostate cancer, while Asian and Native American men have the lowest rates. In addition, there is some evidence that a diet higher in fat, especially animal fat, may

increase the risk of prostate cancer.

4. How are PSA test results reported?

PSA test results report the level of PSA detected in the blood. The test results are usually reported as nanograms of PSA per milliliter (ng/ml) of blood. In the past, most doctors considered PSA values below 4.0 ng/ml as normal. However, recent research found prostate cancer in men with PSA levels below 4.0 ng/ml (2). Many doctors are now using the following ranges, with some variation:

- 0 to 2.5 ng/ml is low
- 2.6 to 10 ng/ml is slightly to moderately elevated
- 10 to 19.9 ng/ml is moderately elevated
- 20 ng/ml or more is significantly elevated

There is no specific normal or abnormal PSA level. However, the higher a man's PSA level, the more likely it is that cancer is present. But because various factors can cause PSA levels to fluctuate, one abnormal PSA test does not necessarily indicate a need for other diagnostic tests. When PSA levels continue to rise over time, other tests may be needed.

5. What if the test results show an elevated PSA level?

A man should discuss elevated PSA test results with his doctor. There are many possible reasons for an elevated PSA level, including prostate cancer, benign prostate enlargement, inflammation, infection, age, and race.

If no other symptoms suggest cancer, the doctor may recommend repeating DRE and PSA tests regularly to watch for any changes. If a man's PSA levels have been increasing or if a suspicious lump is detected during the DRE, the doctor may recommend other tests to determine if there is cancer or another problem in the prostate. A urine test may be used to detect a urinary tract infection or blood in the urine. The doctor may recommend imaging tests, such as ultrasound (a test in which high-frequency sound waves are used to obtain images of the kidneys and bladder), x-rays, or cystoscopy (a procedure in which a doctor looks into the urethra and bladder through a thin, lighted tube). Medicine or surgery may be recommended if the problem is BPH or an infection.

If cancer is suspected, a biopsy is needed to determine if cancer is present in the prostate. During a biopsy, samples of prostate tissue are removed, usually with a needle, and viewed under a microscope. The doctor may use ultrasound to view the prostate during the biopsy, but ultrasound cannot be used alone to tell if cancer is present.

6. What are some of the limitations of the PSA test?

- **Detection does not always mean saving lives:** Even though the PSA test can detect small tumors, finding a small tumor does not necessarily reduce a man's chance of dying from prostate cancer. PSA testing may identify very slow-growing tumors that are unlikely to threaten a man's life. Also, PSA testing may not help a man with a fast-growing or aggressive cancer that has already spread to other parts of his body before being detected.

- **False positive tests:** False positive test results (also called false positives) occur when the PSA level is elevated but no cancer is actually present. False positives may lead to additional medical procedures that have potential risks and significant financial costs and can create anxiety for the patient and his family. Most men with an elevated PSA test turn out ***not*** to have cancer; only 25 to 30 percent of men who have a biopsy due to elevated PSA levels actually have prostate cancer (3).

- **False negative tests:** False negative test results (also called false negatives) occur when the PSA level is in the normal range even though prostate cancer is actually present. Most prostate cancers are slow-growing and may exist for decades before they are large enough to cause symptoms. Subsequent PSA tests may indicate a problem before the disease progresses significantly.

7. Why is the PSA test controversial?

Using the PSA test to screen men for prostate cancer is controversial because it is not yet known if this test actually saves lives. Moreover, it is not clear if the benefits of PSA screening outweigh the risks of follow-up diagnostic tests and cancer treatments. For example, the PSA test may detect small cancers that would never become life threatening. This situation, called overdiagnosis, puts men at risk for complications from unnecessary treatment such as surgery or radiation.

The procedure used to diagnose prostate cancer (prostate biopsy) may cause side effects, including bleeding and infection. Prostate cancer treatment may cause incontinence (inability to control urine flow) and erectile dysfunction (erections inadequate for intercourse). For these reasons, it is important that the benefits and risks of diagnostic procedures and treatment be taken into account when considering whether to undertake prostate cancer screening.

8. What research is being done to validate and improve the PSA test?

The benefits of screening for prostate cancer are still being studied. The National Cancer Institute (NCI) is currently conducting the

Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, or PLCO trial, to determine if certain screening tests reduce the number of deaths from these cancers. The DRE and PSA are being studied to determine whether yearly screening to detect prostate cancer will decrease a man's chance of dying from prostate cancer. Full results from this study are expected in several years. Scientists also are researching ways to distinguish between cancerous and benign conditions, and between slow-growing cancers and fast-growing, potentially lethal cancers. Some of the methods being studied are:

- **PSA velocity:** PSA velocity is based on changes in PSA levels over time. A sharp rise in the PSA level raises the suspicion of cancer.

- **Age-adjusted PSA:** Age is an important factor in increasing PSA levels. For this reason, some doctors use age-adjusted PSA levels to determine when diagnostic tests are needed. When age-adjusted PSA levels are used, a different PSA level is defined as normal for each 10-year age group. Doctors who use this method generally suggest that men younger than age 50 should have a PSA level below 2.4 ng/ml, while a PSA level up to 6.5 ng/ml would be considered normal for men in their 70s. Doctors do not agree about the accuracy and usefulness of age-adjusted PSA levels.

- **PSA density:** PSA density considers the relationship of the PSA level to the size of the prostate. In other words, an elevated PSA might not arouse suspicion if a man has a very enlarged prostate. The use of PSA density to interpret PSA results is controversial because cancer might be overlooked in a man with an enlarged prostate.

- **Free versus attached PSA:** PSA circulates in the blood in two forms: free or attached to a protein molecule. With benign prostate conditions, there is more free PSA, while cancer produces more of the attached form. Researchers are exploring different ways to measure PSA and to compare these measurements to determine if cancer is present.

- **Alteration of PSA cutoff level:** Some researchers have suggested lowering the cutoff levels that determine if a PSA measurement is normal or elevated. For example, a number of studies have used cutoff levels of 2.5 or 3.0 ng/ml (rather than 4.0 ng/ml). In such studies, PSA measurements above 2.5 or 3.0 ng/ml are considered elevated. Researchers hope that using these lower cutoff levels will increase the chance of detecting prostate cancer; however, this method may also increase overdiagnosis and false positive test results and lead to unnecessary medical procedures.

- **Protein patterns:** Scientists are also studying a test that can

rapidly analyze the patterns of various proteins in the blood. Researchers hope that this technique can determine if a biopsy is necessary when a person has a slightly elevated PSA level or an abnormal DRE.

For additional information about prostate cancer, contact the NCI's Cancer Information Service (see below).

Selected References

1. Ries LAG, Eisner MP, Kosary CL, et al. (eds). *SEER Cancer Statistics Review, 1975–2001,* National Cancer Institute. Bethesda, MD, 2004 (http://seer.cancer.gov/csr/1975_2001).

2. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level =4.0 ng per milliliter. *The New England Journal of Medicine* 2004; 350(22):2239–2246.

3. Keetch DW, Catalona WJ, Smith DS. Serial prostatic biopsies in men with persistently elevated serum prostate specific antigen values. *The Journal of Urology* 1994; 151(6):1571–1574.

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Related Resources

Publications (available at http://www.cancer.gov/publications)

- Cancer Facts 4.20, *Selenium and Vitamin E Cancer Prevention Trial (SELECT): Questions and Answers*
- Cancer Facts 5.18, *Tumor Markers*
- Cancer Facts 5.23, *Early Prostate Cancer: Questions and Answers*
- *Understanding Prostate Changes: A Health Guide for All Men*
- *What You Need To Know About™ Prostate Cancer*

National Cancer Institute (NCI) Resources

Cancer Information Service (toll-free)
Telephone: 1–800–4–CANCER (1–800–422–6237)
TTY: 1–800–332–8615

Online
NCI's Web site: http://www.cancer.gov
LiveHelp, NCI's live online assistance:
https://cissecure.nci.nih.gov/livehelp/welcome.asp